IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

WOLLIN, Stefan-Lutz

Serial No.: 10/560,116 Art Unit: 1654

Filed: December 9, 2005 Examiner: KHANNA, H.

For: **COMPOSITION COMPRISING A PULMONARY SURFACTANT AND A PDE5 INHIBITOR FOR THE TREATMENT OF LUNG DISEASES**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Declaration Under 37 CFR 1.132

1. I, Dr. Dietrich Häfner, declare and say:

1.1. That I am a citizen of the Federal Republic of Germany, residing at Beethovenstrasse 5, 78464 Konstanz, Germany.

1.2. That I have expert knowledge of the subject matter of the captioned application for U.S. Letters Patent.

1.3. That, I have studied medicine at the Philipps University of Marburg (1980-1986) where I also made my doctoral thesis (1988). Since 1986 I have the licence to practice medicine. Since 1992 I am graduated as expert in pharmacology and toxicology by the German Medical Association In 2003 I received the EUCOR/ECPM Diploma in Pharmaceutical Medicine. Since 2005 I am an Assistant Professor (Privat-Dozent) for pharmacology and toxicology at the Justus-Liebig-University Gießen.

1.4. That, I am currently working as a Medical Expert at Altana Pharma, Konstanz/Germany. I started as head of a pharmacological laboratory in 1988 at Byk Gulden Pharmaceuticals in Konstanz/Germany (now operating under Altana Pharma) and switched in 1999 to Clinical Research at Byk Gulden Pharmaceuticals in Konstanz/Germany (now operating under Altana Pharma). In 2001 I became the Sponsor's Responsible Medical Officer first for an Intensive Care product and since 2003 for an asthma drug.

2. Summary and Traversal of the 35 U.S.C. §103 rejections

2.1 I have intensively studied the Office Action dated October 17, 2006, as well as the cited prior art:
a) Wilkins, "Acute Respiratory Failure: Diagnosis, Monitoring, Techniques, and Therapeutics", Clinical Techniques in Equine Practice, (2003), vol. 2, pages 56-66; and
b) Häfner, et al., PCT Publication WO01/76619 A1,
and I am aware that the examiner has rejected claims 3-5, 7-12, 15 and 34-35 under 35 U.S.C. §103(a) as being unpatentable over Wilkins in view of Häfner, et al.

2.2 Claim 3 of the present invention in the actual wording relates to a method for preventing or reducing the onset of symptoms of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental, or treating or reducing the severity of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental in a patient, comprising administering intratracheally or intrabronchially to a patient in need thereof an effective amount of (1) a pulmonary surfactant and (2) SILDENAFIL or a pharmaceutically acceptable salt thereof.

2.3 Wilkins at page 59, first column, discloses that intravenous administration of sildenafil, a PDE5 inhibitor, is being

investigated in human infants with Persistent Pulmonary Hypertension of the Newborn (PPHN). Wilkins states that intravenous administration of sildenafil has been investigated as a pulmonary vasodilator in a model of meconium aspiration syndrome in piglets, and the increase in pulmonary vascular resistance was reversed within 1 hour of commencing the intravenous infusion of sildenafil. Wilkins at page 65, first column, also discloses that inactivation of pulmonary surfactant may be important in acute respiratory failure, acute lung injury, and acute respiratory distress syndrome (RDS), and that treatment of surfactant dysfunction by instilling exogenous surfactants may improve gas exchange and pulmonary mechanics. Wilkins does not disclose a treatment of pulmonary disease by administration of a pulmonary surfactant and a PDE5 inhibitor.

2.4. Häfner et al. disclose a method of using recombinant pulmonary surfactant proteins designated as lusupultide for treating pulmonary diseases including ALI, ARDS, acute respiratory insufficiency, pneumonias, nasocomial infections, and SIRS (page 3, second paragraph). Häfner, et al. does not teach the administration of a PDE5 inhibitor.

2.5 The Examiner alleges in the rejection of claims 3-5, 7-12, 15 and 34-35 under 35 U.S.C. §103(a) as being unpatentable over Wilkins in view of Häfner et al. that one of ordinary skill in the art would have been motivated to treat pulmonary diseases using the co-administration of both sildenafil and lusupultide, in view of Wilkins and Häfner which teach the individual use of the two compounds to treat pulmonary diseases. Applicant's traversal and reasons why the rejection fails to establish a *prima facie* case of obviousness are presented in the attached amendment and response to the office action. In part, there is no motivation provided in the cited documents in combination with the skill of the artisan to co-

administer either intratracheally or intrabracheally both the pulmonary surfactant and sildenafil.

2.6 Furthermore, presented herewith, in Appendix A, is a compilation of methods and data gathered during studies in our laboratory of the combined effect of the pulmonary surfactant Venticute with a PDE5 inhibitor in a reoxygenation of a rat lung lavage model. I hereby declare and state I have either conducted or supervised the work described here and in Appendix A. This data unequivocally and unexpectedly demonstrates that intratracheal (i.t.) administration of a pulmonary surfactant preparation comprising Venticute in combination with PDE5 inhibitor Sildenafil results in an unexpected superadditive effective of the two components when administered in combination. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 3-5, 7-12, 15, and 34-35 under 35 USC §103(a).

2.7 The Examiner has alleged that the presently pending claims are obvious in view of the disclosure of these references, however the cited references do not establish a *prima facie* case of obviousness for the reasons Applicant presents in the accompanying amendment and response to the Office Action dated October 17, 2006.

2.8 If, however, the Examiner insists on maintaining that the presently pending claims are obvious in view of the deficient teachings of the cited references, applicant again respectfully draws the Examiner's attention to Figures 1 and 2 of Appendix A which unexpectedly demonstrates a much higher reoxygenation due to intratracheal (i.t.) administration of a pulmonary surfactant in combination with Sildenafil. Neither the prior art nor one of skill in the art would have expected such a superadditive effect of combined administration of

Sildenafil and a pulmonary surfactant. Thus, the data submitted herewith in Appendix A unexpectedly shows that the presently claimed method for preventing or reducing the onset of symptoms of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental, or treating or reducing the severity of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental in a patient, comprising administering intratracheally or intrabronchially to a patient in need thereof an effective amount of (1) a pulmonary surfactant and (2) SILDENAFIL or a pharmaceutically acceptable salt thereof results in a superadditive effect of combined administration of Sildenafil with a pulmonary surfactant. These results are unexpected in view of the teachings of the prior art which merely shows that a pulmonary surfactant and Sildenafil can each be used separaetley to treat various pulmonary disorders using different routes of administration than those presently claimed. As such, a person of ordinary skill in the art would not expect that combining these two different treatments in a different route of administration would provide synergistic effects in treating a disease by preventing or reducing the onset of symptoms of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental, or treating or reducing the severity of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental in a patient. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 3-5, 7-12, 15, and 34-35 under 35 USC §103(a).

3. The undersigned Declarant declares further that all statements made herein and in the Appendix of his own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issuing thereon.

Signed at Constance,
Federal Republic of Germany,

January 09, 2007.

Dietrich Häfner

Dr. Dietrich Häfner

APPENDIX A

1. Anesthetized Sprague Dawley rats are artificially ventilated with pure oxygen and a positive endexiratory pressure (PEEP; in order to ensure oxygenation of the rats) and lavaged until their endogenous lung surfactant were washed out [D. Illifner, R. Beume, U. Killian, O. Kraznai and Burkhard Lachmann: Dose-response comparison of five lung surfactant (LSF) preparations in an animal model of adult respiratory distress syndrome (ARDS); D. Hafner, P.-G. Germann, D. Hauschke, Pulmonary Pharmacology (1994) 7, 319-332]. This was manifested by the fact that in the animals the preliminary values of the arterial oxygen partial pressure (PaO_2) of 500-550 mmHg (in the case of pure oxygen ventilation and PEEP) decreased to values of 50-110 mmHg. Animals of the control group which were not treated with lung surfactant remained with their PaO_2 at these low values throughout the observation period. 60 minutes after the PaO_2 decreased to these values, lung surfactant Venticute or lung surfactant Venticute together with a PDE5 inhibitor was instilled intratracheally (i.t.) or perorally (p.o.). Venticute was administered at a dose of 12.5 mgPL/kg. A PDE5 inhibitor selected from Sildenafil, Vardenafil, or Tadalfil was administered at a dose of 100nM. The blood gases were determined 30 minutes before, and at 0, 30, 60, 90, 120, 150, 180, and 210 minutes after, instillation.

2. In Figure 1 below, the effects of intratracheal (i.t.) administration of Venticute and Sildenafil, both alone and in combination, were measured.

Figure 1.

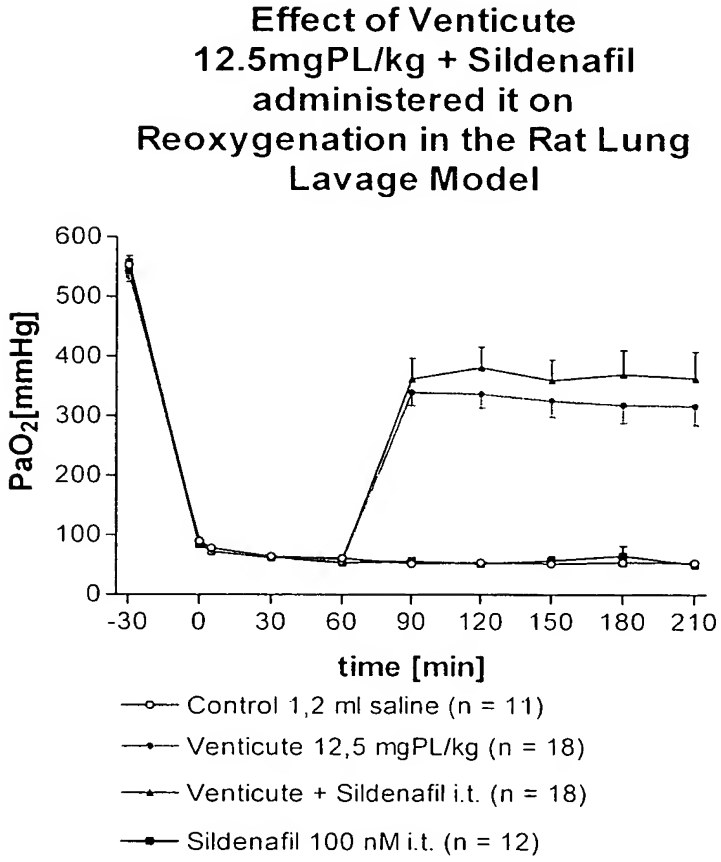


Table 1	Control	Sildenafil i.t.	Venticute	Venticute + Sildenafil i.t.
PaO_2 at 120 min Mean ± SEM	54.1 ± 3.9	51.8 ± 4.8	337.0 ± 23.2	381.9 ± 34.3

The average values (± standard error of the mean [SEM]) of the PaO_2 are indicated in mmHg for the time indicated (constant PEEP of 8 cm H_2O) after intratracheal instillation of the test composition after the last

lavage. The untreated control composition was a lavage of 1.2 ml saline only to one set of animals. Venticute alone was administered to another set of animals. Sildenafil alone was administered to another set of animals. And, Venticute combined with Sildenafil was administered to another set of animals. It can be seen from the Table 1that the sole administration of Sildenafil has no influence on the PaO_2 as compared to the untreated control animals. The administration of lung surfactant Venticute leads to a rise in the PaO_2. Unexpectedly, the i.t. administration of Sildenafil together with the low dose (12.5 mgPL/kg) of lung surfactant Venticute results in an further increase in reoxygenation to PaO_2 values higher than Ventivute alone. The expected additive effect of Venticute and Sildenafil on combined reoxygenation would be calculated as:

[(PaO_2 Venticute alone)]

Plus

[(PaO_2 Sildenafil alone) - (PaO_2 saline control)]

Thus, at 120 minutes we calculate expected combined effect as:

[(PaO_2 Venticute alone)] = 337.0 mmHg

Plus

[(PaO_2 Sildenafil alone = 51.8 mmHg) - (PaO_2 saline control = 54.1) = (-2.3 mmHg] = expected combined effect of 334.7mmHg.

Thus, the expected reoxygenation of combined i.t. administration of Venticute and Sildenafil is calculated as 334.7mmHg, and one would expect no additional reoxygenation by the i.t. co-administration of Sildenafil with the Venticute composition. However, the resulting reoxygenation of 381.9 mmHg for the combined i.t. administration of Venticute and Silde-

nafil was significantly greater than unexpected, and shows a superadditive effect of Venticute and Sildenafil in the rat lung lavage model.

3. In Figure 2 below, the effects of peroral (p.o.) administration of Venticute and Sildenafil, both alone and in combination, were measured.

Figure 2.

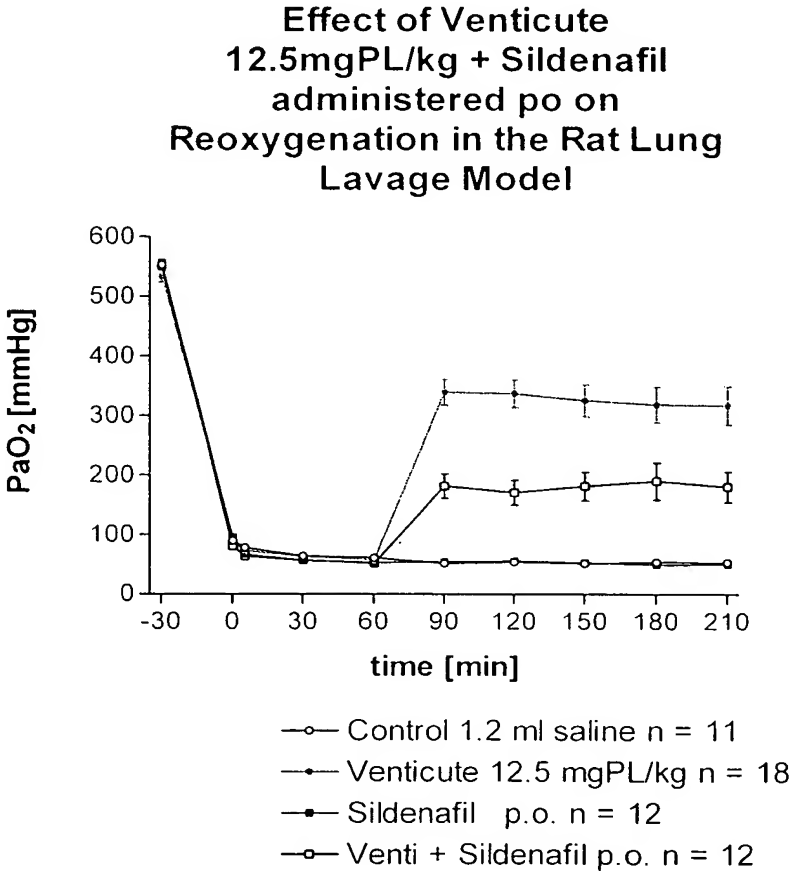


Table 2	Control	Sildenafil p.o.	Venticute	Venticute + Sildenafil p.o.
PaO_2 at 120 min Mean ± SEM	54.0 ± 3.6	49.8 ± 2.9	318.6 ± 29.7	190.0 ± 31.4

The average values (± standard error of the mean [SEM]) of the PaO_2 are indicated in mmHg for the time indicated (constant PEEP of 8 cm H_2O)

after peroral (p.o.) instillation of the test composition after the last lavage. The untreated control composition was a lavage of 1.2 ml saline only to one set of animals. Venticute alone was administered to another set of animals. Sildenafil alone was administered to another set of animals. And, Venticute combined with Sildenafil was administered to another set of animals. It can be seen from the Table 2 that the sole administration of Sildenafil has no influence on the PaO_2 as compared to the untreated control animals. The administration of lung surfactant Venticute leads to a rise in the PaO_2. Unexpectedly, the p.o. administration of Sildenafil together with the low dose (12.5 mgPL/kg) of lung surfactant Venticute results in an further increase in reoxygenation to PaO_2 values higher than Venticute alone. The expected additive effect of Venticute and Sildenafil on combined reoxygenation would be calculated as:

[(PaO_2 Venticute alone)]

Plus

[(PaO_2 Sildenafil alone) - (PaO_2 saline control)]

Thus, at 120 minutes we calculate expected combined effect as:

[(PaO_2 Venticute alone)] = 318.6 mmHg

Plus

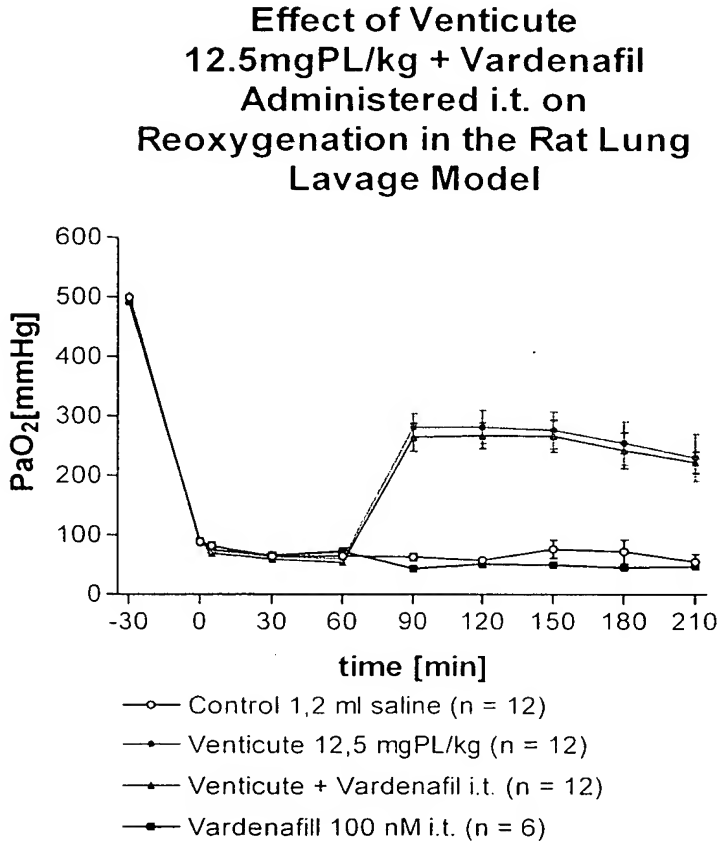
[(PaO_2 Sildenafil alone = 49.8 mmHg) - (PaO_2 saline control = 54.0) = 4.2 mmHg] = expected combined effect of 314.4 mmHg.

Thus, the expected reoxygenation of combined p.o. administration of Venticute and Sildenafil is calculated as 314.4 mmHg, and one would expect no additional reoxygenation by the p.o. co-administration of Sildenafil with the Venticute composition. The resulting reoxygenation of 190.0 mmHg for the combined p.o. administration of Venticute and Sildenafil was significantly lower than expected, and shows no superadditive effect of Venticute and Sildenafil in the rat lung lavage model. This

supports that the i.t. co-administration is the preferred mode of administration.

4. In Figure 3 below, the effects of intratracheal (i.t.) administration of Venticute and Vardenafil, both alone and in combination, were measured.

Figure 3.

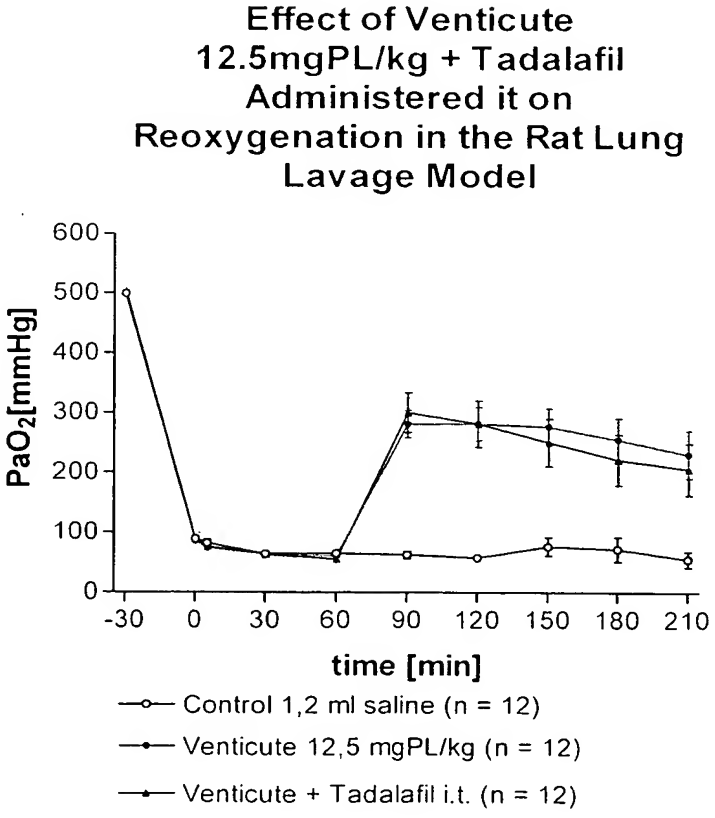


The average values (± standard error of the mean) of the PaO_2 are indicated in mmHg for the time indicated (constant PEEP of 8 cm H_2O) after intratracheal instillation of the test composition after the last lavage. The untreated control composition was a lavage of 1.2 ml saline only to one set of animals. Venticute alone was administered to another set of animals. Vardenafil alone was administered to another set of animals. And, Venticute combined with Vardenafil was administered to another set of animals. It can be seen from the figure that the sole ad-

ministration of Vardenafil had a small influence on the PaO_2 as compared to the untreated control animals. Similarly, administration of Vardenafil in combination with Venticute had only a small influence on the PaO_2 as compared to administration of Venticute alone. Accordingly, unlike the combination of Venticute and Sildenafil, the combination of Venticute and Vardenafil did not exhibit a superadditive effect on reoxygenation in this rat lung lavage model.

5. In Figure 4 below, the effects of intratracheal (i.t.) combined administration of Venticute and Tadalafil was measured, and compared to sole administration of Venticute.

Figure 4.



The average values (± standard error of the mean) of the PaO_2 are indicated in mmHg for the time indicated (constant PEEP of 8 cm H_2O) after

intratracheal instillation of the test composition after the last lavage. The untreated control composition was a lavage of 1.2 ml saline only to one set of animals. Venticute alone was administered to another set of animals, and Venticute combined with Tadalafil was administered to another set of animals. It can be seen from the figure that administration of Tadalafil in combination with Venticute had only a small influence on the PaO_2 as compared to administration of Venticute alone. Accordingly, unlike the combination of Venticute and Sildenafil, the combination of Venticute and Tadalafil did not exhibit a superadditive effect on reoxygenation in this rat lung lavage model.